

Urethritis due to *Chlamydia trachomatis*

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SUMMARY Ninety-five men suffering from gonococcal urethritis were treated and observed. Forty-nine developed postgonococcal non-specific urethritis (PGU). Seventeen men were demonstrated to be free from PGU after careful observation; these formed a control group. *Chlamydia trachomatis* was isolated from urethral material from 26 (53%) of the PGU group but from none of the controls. This difference was highly significant ($P < 0.001$). It confirms that *C. trachomatis* is a pathogen in the urethra. The presence of specific IgM antibody to *C. trachomatis* in serum from some men developing PGU, from whom that organism was isolated, suggests that the infection was recent in those cases. *Ureaplasma urealyticum* (T strain mycoplasma) was isolated from urethral material taken from 22 (45%) of the 49 men in the PGU group, and from 12 (71%) of 17 in the control group. *Mycoplasma hominis* was isolated from 10 (20%) of the 49 men in the PGU group, and from four (24%) of the 17 men in the control group. Thus, no evidence was obtained that mycoplasmas (*U. urealyticum*, *M. hominis*) are pathogenic in the urethra.

Introduction

In a series of studies since 1962 by this research group at The London Hospital and the Institute of Ophthalmology, *Chlamydia trachomatis* has been isolated from urethral material from men with non-specific urethritis, but not from those without urethritis. For this reason we considered *C. trachomatis* to be pathogenic in the urethra, as in the conjunctiva and, as evidence suggests it is, in the cervix and the anorectal canal in women (Dunlop, 1975).

Urethral material was obtained initially by means of a curette (Dunlop *et al.*, 1965), but when sensitive methods using cell-culture systems became available, good results were obtained using a small endo-urethral swab made to our design (Dunlop *et al.*, 1972). These swabs were used for repeated tests of urethral material in this controlled study.

More than half the number of men treated for gonococcal urethritis with the penicillins or aminoglycosides, and who are then carefully followed-up, can be expected to develop postgonococcal non-specific urethritis (PGU). In a study of 120 men initially treated with procaine penicillin by intramuscular injection for gonococcal urethritis, 35 had developed PGU within a month of treatment. 29 of the remainder remained free during careful observation for a month (Hare *et al.*, 1969). These urethritis-free men constituted a control group. The incidence of mycoplasmas in urethral material was similar in the two groups, so there was no evidence that the mycoplasmas were a cause of urethritis.

This study is a repetition of the previous controlled study with the addition of repeated tests for *Chlamydia*.

Patients and methods

Starting on 3 March 1972 men who presented at the Whitechapel Clinic with gonococcal urethritis were seen initially and at follow-up by one of us (JV-J).

Ninety-five men were studied. Typical Gram-negative intracellular diplococci were present in a

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smear of the urethral secretion in each case, and *Neisseria gonorrhoeae* was grown from 83 of the 95 men; in a further six *Neisseria*-positive cases sugar-fermentation reactions were not obtained so these organisms were reported as 'presumptive gonococci'.

Kanamycin, active against gonococci, has an antimycoplasmal action *in vitro*, but it does not have an antichlamydial action; the converse applies to penicillin. Accordingly, 2 g of kanamycin by intramuscular injection was given to alternate patients; the others received 2.4 megaunits of procaine penicillin by intramuscular injection, with probenecid 2 g by mouth.

Men were excluded from the study if they were unable to attend for follow-up. Men who were receiving antibiotics additional to penicillin or kanamycin, or both, or chemotherapeutic agents other than metronidazole, were also excluded.

At each visit patients were asked about symptoms and if they had had further sexual intercourse; the details were recorded. If they had had further intercourse they were not excluded as they had been in the previous study (Hare *et al.*, 1969).

Methods of investigation were as previously described (Hare *et al.*, 1969) with the addition of the collection of material for culture for *Chlamydia* from the urethra with endourethral swabs (Dunlop *et al.*, 1972). This was carried out before treatment, and was to be repeated 3 to 4, and 7, 14, and 28 days after treatment. After the first post-treatment investigations, patients were instructed to attend for assessment of the overnight urethral secretion at each visit.

Cultures for *Chlamydia* were carried out in irradiated McCoy cells using the modified technique described by Darougar *et al.* (1971).

Sera were tested for antichlamydial type-specific antibody using the microimmunofluorescence (micro-IF) test (Treharne *et al.*, 1977) of Wang and Grayston and for antichlamydial group antibody by the lymphogranuloma venereum complement-fixation test (LGVCFT).

Blood was taken for these additional tests at the first visit, and on the 14th and 28th days.

As before (Hare *et al.*, 1969), to avoid possible bias by the clinical or laboratory staff, the diagnosis of PGU or of a normal urethra was made on routine urethral smears and negative cultures for gonococci, before the results of cultures for *Chlamydia* and for mycoplasmas were available.

Results

TOTAL INCIDENCE OF MICRO-ORGANISMS

C. trachomatis was isolated from urethral material on one or more occasions from 30 (32%) of the 95

men, as were *Ureaplasma urealyticum* (T strain mycoplasma) from 43 (45%) and *Mycoplasma hominis* from 20 (21%). Of 11 *Chlamydia*-positive patients treated with penicillin, three became positive after treatment; of 19 such patients treated with kanamycin, seven became positive after treatment.

DEVELOPMENT OF PGU AND THE COLLECTION OF THE URETHRITIS-FREE CONTROL GROUP

Forty-nine of the 95 men developed PGU. This condition was diagnosed in 46 of the cases on the seventh or 14th day after treatment for gonorrhoea. In three cases diagnosed on the 28th day, examination on the seventh and 14th day had been missed in two, and on the 14th day in the remaining one. This suggests that four urethritis-free patients observed for only 14 days, can be considered together with the 13 such patients observed for the full 28 days. Thus in all 17 urethritis-free men were taken as controls.

ISOLATION OF MICRO-ORGANISMS FROM PGU GROUP AND CONTROL GROUP

C. trachomatis was isolated from 26 (53%) of the 49 men who developed PGU. *C. trachomatis* was not isolated from the 17 control men (Table 1). This difference in the isolation rates is highly significant ($\chi^2 = 14.8$ (with continuity correction) $P < 0.001$). If the control group is restricted to the 13 men observed for the full 28 days, the difference in isolation rates is still of the same order of significance ($P < 0.001$). *U. urealyticum* was isolated from 22 (45%) of the 49 men with PGU, compared with 12 (71%) of the 17 control patients. *M. hominis* was isolated from 10 (20%) of the 49 men with PGU, compared with four (24%) of the 17 controls. In seven of these 49 cases, both mycoplasmas were isolated together, compared with four of the 17 controls (Table 1). In 11 (22%) of these 49 cases neither *U. urealyticum* nor *C. trachomatis* was isolated, *M. hominis* was isolated in one.

Table 1 *Chlamydia trachomatis* and mycoplasmas in urethral material from men with PGU and controls

Group	PGU		Control	
	No.	%	No.	%
No.	49	100	17	100
<i>C. trachomatis</i> isolated	26*	53	0**	0
Mycoplasmas isolated				
<i>U. urealyticum</i> alone or with				
<i>M. hominis</i>	22†	45	12‡	71
* <i>M. hominis</i> alone or with				
<i>U. urealyticum</i>	10§	20	4¶	24
Both together	7	14	4	24

*50 positive tests of 132 †38 positive tests of 91 §16 positive tests of 83

**61 tests negative ‡19 positive tests of 51 ¶6 positive tests of 51

SEROLOGICAL TESTS

The LGVCFT was positive in only one case (Table 2); in contrast the micro-IF test for type-specific IgG antibody to *C. trachomatis* was positive (titre ≥ 1 in 8) in the cases of 11 (48%) of 23 patients in the PGU *C. trachomatis*-positive group, six of 21 (29%) in the *C. trachomatis*-negative group, and in three of 14 in the control group. In no case was there a rise in titre of antichlamydial IgG. The micro-IF test for antichlamydial IgM antibody was positive in eight (73%) of the 11 micro-IF-positive cases in the PGU *C. trachomatis*-positive group, in one of the six micro-IF-positive cases in the PGU *C. trachomatis*-negative group, and in none of the three micro-IF-positive cases in the control group. In the PGU *C. trachomatis*-positive group two patients showed a rise in anti-IgM micro-IF titre (twofold and fourfold); two other patients showed a fourfold decline in titre. There was no change in titre in the PGU *C. trachomatis*-negative group or in the control group.

Table 2 Results of serological tests for antichlamydial antibody in men with PGU and controls

Group	LGVCFT			Micro-IF		
	No. tested	Positive		No. tested	Positive	
		No.	%		No.	%
PGU						
<i>C. trachomatis</i> positive	26	0	0	23	11*†	48
<i>C. trachomatis</i> negative	23	1	4	21	6‡	29
Controls	16	0	0	14	3§	21

*One additional patient had a >fourfold rise of antibody titre to IOL-207 at 14 days when he had developed Reiter's disease.

†IgM positive 8/11 (73%)

‡IgM positive 1/6 (17%)

§IgM positive 0/3

Two isolates of *C. trachomatis* were serotyped. One was Type K, the other Type F. Serum from each patient concerned had a titre of 1 in 64 to the homologous serotype. In addition, one patient (treated with kanamycin) had developed a fourfold rise in titre of type-specific IgG antibody to another *Chlamydia* (IOL-207) with some subgroup B properties (Dwyer *et al.*, 1972) at two weeks when he developed Reiter's disease; urethral tests for *Chlamydia* (previously negative) were then positive. This agent could not be grown for typing.

Other findings, including the differences between the kanamycin and penicillin-treated patients, will be considered further elsewhere.

Discussion

Oriel *et al.* (1972), using a cell-culture technique, did not isolate *Chlamydia* from single specimens of

urethral material collected with a curette from each of 31 men without urethritis as shown by normal overnight urethral secretion. However, the difficulty in selecting a suitable control group is shown by the fact that of the 34 men from whom the 31 controls were selected, one had never had sexual intercourse, three had not had intercourse during the previous three months, and a further 10 admitted to intercourse with a regular partner only during that time.

Holmes *et al.* (1975) carried out a similar study. They re-examined 33 men after treatment of gonorrhoea of whom 20 had PGU, including four men with pyuria but no discharge. *C. trachomatis* was isolated from urethral material collected with an endourethral swab from 11 of these 20 men either initially or at re-examination, or on both occasions. Of 13 men without PGU *C. trachomatis* was not isolated initially or at re-examination. Results of cultures for mycoplasmas were reported separately for the men with and without PGU, but at re-examination only *U. urealyticum* was isolated from five, and *M. hominis* from two of the men in the PGU group. *U. urealyticum* was isolated from five and *M. hominis* from five of the 13 men without PGU. Although the initial mycoplasma results were not given for the two groups, the findings are similar to those in the present study. Re-examination was at one to six weeks after treatment for gonorrhoea which may account for the increase in titre of antibody measured by the micro-IF test that was found in some cases.

Oriel *et al.* (1975) collected urethral material with meatal swabs for culture for *Chlamydia*. Forty-four men who presented because of gonococcal urethritis were tested before and after treatment with gentamicin; 27 developed PGU during two weeks' observation. *C. trachomatis* was isolated from 15 men, all of whom developed PGU, and all of whom had antichlamydial antibody detected by an indirect FA test at a titre of 1 in 16 or greater. *C. trachomatis* was not isolated from the 18 men who did not have PGU two weeks after treatment (one had had PGU at one week); 11 of these men were sero-positive.

The findings in the current study confirm that *C. trachomatis* is a pathogen in the urethra of man. This was shown by the isolation of *C. trachomatis* from urethral material from men who developed PGU, and by repeated failure to isolate this agent from the control group of men free from PGU.

Although there is no evidence from the previous study (Hare *et al.*, 1969) or this one that *U. urealyticum* or *M. hominis* is pathogenic in the urethra, it is possible that the isolates of *U. urealyticum* from the PGU group might conceivably have included pathogenic strains which were not present in the

isolates obtained with at least equal frequency from the control groups.

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